Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	09/458,014	DUMAS ET AL.	
	Examiner	Art Unit	
	Yong S. Chong	1617	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 03 August 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-4,8,28,30,38,44,45,50,51,55 and 58*.
   Claim(s) withdrawn from consideration: *53*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

/Yong S. Chong/
Primary Examiner, Art Unit 1617

Continuation of 11. does NOT place the application in condition for allowance because: Applicant's arguments have been fully considered but found not persuasive for reasons of record. The same reasoning set forth in the last Office Action applies here and will be repeated. Applicant argues that the specification provides more than it needs to satisfy the requirement of 112, first paragraph. For example, general and specific methods of preparing the compounds are given on pg. 21-23, 27-71, and in the examples. Dosage forms, ranges, and methods of administration are given on pg. 23-26. Methods for assessing the activity of the compounds via in vitro raf Kinase assays and in vivo assays are provided on pg. 103-104. The specification also discloses that inhibitors of p38 are active in animal models of TNFα production, including a murine lipopolysaccharide (LPS) model of TNFα production.

This is not persuasive because the specification does not provide any experimentation of any compounds in an accepted specific rheumatoid arthritis assay. Additionally, the specification does not provide an assertion that any of the referenced articles specifically describe the inhibition of TNFα, via inhibition of p38 kinase, leads to the treatment of rheumatoid arthritis. The specification merely states that a link exists between TNFα production and/or signaling to a number of diseases including rheumatoid arthritis. What is missing from the specification is sufficient direction and guidance for determining which compounds of formula I that are found to inhibit p38 kinase activity do so in a manner sufficient to inhibit TNFα to a degree that causes a therapeutic effect in rheumatoid arthritis as claimed. Without this guidance, undue experimentation of a skilled artisan would be required to make and use the claimed invention.

Applicants argue against the enablement rejection by claiming that a link exists between TNFα and rheumatoid arthritis, highlighted by the Badger reference. Applicants also corroborate their argument by referring to the in vitro raf kinase assays and in vivo assays in the specification, which is allegedly routine in the field to correlate inhibition of p38 to therapeutic treatment of various diseases. Examiner was reminded that no objective evidence has been presented and also that an example is not required for compliance with an enablement requirement.

This is not persuasive because although there may be link between TNFα or p38 and various diseases this does not correlate to actually treating a disease in any therapeutic sense. In fact, inhibition of p38 is not well known in the field to be correlated to any particular disease.

The specification does not disclose how one of ordinary skill in the art would determine every known disease associated with p38, let alone effectively to treat that disease with a p38 inhibitor considering various factors such as side effects, toxicity, and dosing. There is no indication that such a link actually translates to the treatment of the disease. There is no mention of activity data for any of the disclosed compounds. Further, in vitro raf kinase assays and in vivo assays are not specific to rheumatoid arthritis. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass virtually every disease or disorder that is mediated by p38 kinase.

It is noted that the specification also lacks any factual evidence of actual therapeutic treatment of a disease associated with p38. It is not well established in the field to correlate inhibition of p38 to actual treatment of a disease. Moreover, there is no raw data for any of the disclosed compounds in the examples of the specification. The mice are not disclosed to have a p38 mediated disease or disorder, therefore no disease is being treated in the examples.